REMARKS

Favorable consideration of the subject application is respectfully requested in view of the above amendments and the following remarks. Following the amendments, claims 6, 9-11, 14-16 and 24-27 are under consideration, with claims 6 and 14 being in independent form.

A certified copy of PCT international patent application no. PCT/NZ01/00287, to which the present application claims priority, is submitted herewith.

The specification has been amended to update the status of related patent application no. 09/724,809, and to correct a typographical error in the serial number for the priority PCT patent application. A Patent Application Data Sheet showing the correct serial number for the PCT patent application is filed herewith. Claim 6 has been amended to remove reference to sequences having at least 75% or 90% identity to a SEQ ID NO: 39 or 40, and to clarify that reducing the available amount of the transcriptional regulator of apoptosis results in an increase in apoptotic cell death. Claim 14 has been amended to recite that the transcriptional regulatory of apoptosis is selected from the group consisting of SEQ ID NO: 39 and 40, and to clarify that reducing the available amount of the transcriptional regulator of apoptosis results in an increase in p53-mediated apoptotic cell death. Claims 15 and 16 have been canceled from the application. Claims 25-27, dependent upon claim 14, have been added.

It is urged that support for all the above amendments may be found throughout the specification as originally filed and that none of the above amendments constitute new matter or raise new issues for consideration.

The Examiner objected to the specification as not reciting the status of each related application. This has been corrected.

Rejection under 35 USC §112, first paragraph, Written Description

Claims 6, 9-11, 14-16 and 24 stand rejected under 35 USC §112, first paragraph, as lacking an adequate written description. This rejection is respectfully traversed.

As noted by the Examiner, in order to satisfy the written description requirement, the applicant must convey to one of skill in the art that, at the time the application was filed, he or she was in possession of the claimed invention. Applicants have discovered that it is possible to increase apoptosis, and in particular p53-mediated apoptosis, by reducing the amount of the

known protein YB-1 (SEQ ID NO: 40) or the YB-1 cold shock domain (SEQ ID NO: 39) available to bind to regulatory polynucleotides involved in apoptosis, i.e. by reducing the levels of "free" YB-1 within a population of cells (see page 10, lines 16-29, of the specification). It is this discovery that forms the basis for the claimed invention.

More specifically, amended independent claim 6 is drawn to methods for increasing apoptotic cell death in a population of cells by reducing the amount of a transcriptional regulator of apoptosis (TRA) available to bind to a target polynucleotide in the cells, wherein the TRA is either SEQ ID NO: 39 or 40. Similarly, independent claim 14 is drawn to methods for increasing p53-mediated apoptosis in a cell population by reducing the amount of a TRA available to bind to a target polynucleotide in the cells, wherein the TRA is either SEQ ID NO: 39 or 40.

Examples 2 and 3 of the specification (page 26, line 29 – page 30, line 14) present studies clearly demonstrating an increase in apoptosis following a reduction in the amount of available, or free, YB-1 both *in vitro* in cell culture and *in vivo* in a mouse model. In both these examples, the amount of free YB-1 was reduced by administering either anti-sense oligonucleotides directed against YB-1 or oligonucleotides to which YB-1 had been shown to bind (so-called "decoy oligos"; see Example 1, page 21, line 10 – page 24, line 11, of the specification). The specification thus describes two different methods by which the level of free YB-1 may be reduced. In addition, ten examples of specific antisense oligonucleotides directed against YB-1 are provided (SEQ ID NO: 19-33), together with two examples of specific decoy oligos. All of these are tools which may be employed in the claimed methods. The Examiner states that the "specification discloses ten sequences .... described as being antisense to YB-1, which are not representative of the claimed genus". Applicant notes that the claims are not directed to antisense or decoy oligonucleotides per se but to a method of reducing apoptosis by reducing the amount of free YB-1, which may, for example, be achieved using either antisense oligonucleotides directed against YB-1 or YB-1 decoy oligos.

Applicant is unaware of any requirement in the patent law that the inventor provide a written description of every possible way of carrying out a claimed method, of every possible application of the claimed method, and/or of every possible tool that could be used in the claimed method. Indeed, in Union Oil Co. v. Atlantic Richfield co., 208 F.3d 989 (Fed. Cir 2000) the court held that a "descri[ption] of the exact chemical component of each combination that falls

within the range claims of the ... patent" is not necessary to comply with §112. Rather, the inventor must provide sufficient written description for one of skill in the art to appreciate that the inventor had invented, and was in possession of, the claimed invention (in the present instance methods of reducing apoptosis by reducing the amount of free YB-1 or YB-1 cold shock domain) at the time the application was filed. The instant specification clearly provides a description of the increase in apoptosis following the reduction of the amount of YB-1 or YB-1 cold shock domain available to bind to its target polynucleotide, of methods that may be used to reduce the amount of available YB-1 or YB-1 cold shock domain, and of exemplary antisense and decoy oligonucleotides.

In support of his position, the Examiner cites Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 927, 69USPQ2d 1886, 1895-95 (Fed. Cir. 2004) and Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, the claims at issue were drawn to DNA molecules encoding the genus of mammalian basic fibroblast growth factors (FGFs), however the application only disclosed the amino acid sequence for bovine pituitary FGF and a corresponding theoretical DNA sequence, which was determined to be incorrect. In Univ. of Rochester v. G.D. Searle & Co. the claims were directed to methods for selectively inhibiting the COX-2 (also known as PGHS-2) enzyme by administering a compound that inhibits COX-2. However, in the patent in question "[n]o compounds that will perform the claimed methods are disclosed, nor has any evidence been shown that such a compound was known". In contrast, the instant specification clearly describes several examples of oligonucleotides that can be successfully employed in the claimed methods and provides data demonstrating the effectiveness of these oligonucleotides in the claimed methods. Furthermore, as evidenced by the publication of Ohga et al. (*Cancer Res.* 56:4224-4228, 1996; cited by the Examiner), YB-1 antisense plasmids were known to those of skill in the art by the priority date of the present application.

It is urged that one of skill in the art would appreciate that the inventors were indeed in possession of the claimed invention at the time the application was filed, and that the rejection of the claims under 35 USC §112, first paragraph, as lacking an adequate description may thus be properly withdrawn.

Rejection under 35 USC §112, first paragraph, Enablement

Claims 6, 9-11, 14-16 and 24 stand rejected under 35 USC §112, first paragraph, as lacking an enabling disclosure. Specifically, the Examiner asserts that the specification does not enable methods for increasing apoptotic death *in vivo* in any organism other than a mouse, and does not enable treatment of a disorder. This rejection is respectfully traversed.

As discussed above, the pending claims are drawn to methods of modulating either apoptotic cell death, or p53-mediated apoptotic cell death, by reducing the amount of a TRA available to bind to a target polynucleotide in a cell, wherein the TRA is either YB-1 or the YB-1 cold shock domain. As taught in the specification at page 1, line 23- page 2, line 8, and well-known in the art, an ability to increase apoptotic cell death is desirable in many situations, including, but not limited, to the treatment of cancer (see, Kasibhatla et al., Mol. Cancer Therapeutics 2:573-580, 2003, for a review of apoptosis and cancer treatment; copy enclosed for the Examiner's convenience). The specification discloses two specific methods for reducing the amount of the TRA in a cell, namely by introducing into the cell either antisense oligos to YB-1 or decoy oligos that contain a YB-1 binding site (see, for example, page 12, line 9 – page 13, line 9) and provides studies demonstrating the effectiveness of these methods both *in vitro* and *in vivo* in a mouse model (see, Examples 2 and 3). The Examiner asserts that the specification does not enable the use of antisense or decoy oligonucleotides in therapeutic applications and further that the *in vivo* studies described in the application are not predictive of efficacy in any organism other than the mouse. Applicant respectfully disagrees.

Many groups initially use cultured cells and then mice as pre-clinical models in the development of therapies for human cancers. One example of this is the development of the FDA approved drug Herceptin (Trastuzumab), which is currently used to treat patients with metastatic breast cancer whose tumors overexpress the HER2 protein. Experiments were first performed in cultured cancer cell lines and demonstrated that Herceptin was able to inhibit growth of breast and ovarian cancer cells (Hudziak et al., Mol. Cell. Biol. 1989, 9:1165-72; Lewis et al., Cancer Immunol. Immunother. 1993, 37:255-63; copies enclosed herewith for the Examiner's convenience). Pre-clinical studies were then performed in mouse models, where Herceptin demonstrated a dose-dependent antitumor activity against tumors in mice (Baselja et al., Cancer Res. 1998, 58:2825-31; abstract enclosed herewith for the Examiner's convenience).

Many additional examples of the use of mice as pre-clinical models can be found at the National Cancer Institute's website for Mouse Models of Human Cancers (emice.nci.nih.gov).

Furthermore, in April 1997, before the priority date of the instant application, Webb et al. reported preliminary results from a Phase I study demonstrating the effectiveness of antisense oligonucleotides against BCL-2 in the treatment of patients with non-Hodgkin lymphoma (The Lancet 1997, 349:1137-1141; copy enclosed for the Examiner's convenience). As discussed by Webb et al., over-expression of the BCL-2 gene is known to result in resistance to apoptotic cell death. Webb et al. state that administration of the BCL-2 antisense oligos leads to a down-regulation of BCL-2 expression which in turn leads to increased apoptosis. Webb et al. additionally state that the effectiveness of the antisense oligos against BCL-2 was examined in a mouse model prior to testing in humans. These studies clearly demonstrate that mouse models may be effectively employed to predict the efficacy of new therapeutics in the treatment of humans and further demonstrate the high level of skill in the art at the effective filing date of the instant application.

It is thus urged that one of skill in the art, on being provided with the instant specification, would indeed have been able to practice the claimed methods at the time the application was filed, and that this rejection of the claims under 35 USC §112, first paragraph, may therefore be properly removed.

Rejections under 35 USC §102 and §103

Claims 6, 9, 11 and 24 stand rejected under 35 USC §102(b) as being anticipated by, or alternatively, under 35 USC §103(a) as being obvious over, Wada et al. (J. Biol. Chem. 1995, 270:18007-18012). This rejection is respectfully traversed.

Wada et al. describe studies in which the 5'-upstream region of the FAS gene was fused to the coding sequence of the firefly luciferase gene and the resulting DNA was introduced into HeLa cells. As noted by the Examiner, the 5'-upstream region of the FAS gene contains the sequence of SEQ ID NO: 2 of the present application. Wada et al. do not teach that apoptosis was increased in the transformed HeLa cells. Rather the reference states that the transformed cells were culture for 24 hours before being infected with influenza virus. Lysates of the infected

cells were then prepared at periods of up to 8 hours after infection and the luciferase activity was determined.

As discussed in the specification on page 10, lines 16-29, and as evidenced by the studies described in Example 4 of the specification, the inventors have demonstrated that in order for an increase in apoptosis to occur following introduction of either antisense oligonucleotides against YB-1 or YB-1 decoy oligos to tumor cells, the cells must have wild-type, or functional p53. The HeLa cells employed by Wada et al. have the E67 protein from human papillomavirus (HPV) type 16 that targets p53 for rapid degradation (See, for example, Hoppe-Seyler and Butz, J. Virol., 1993, 67:3111-3117; Minagawa et al., Jpn. J. Cancer Res. 1999, 90:1373-9; copies enclosed for the Examiner's convenience). The p53 pathway is thus compromised in HeLa cells and apoptosis cannot occur via p53. Wada et al. therefore could not have seen apoptosis when treating HeLa cells with the Fas promoter sequence.

It is thus submitted that Wada et al. neither teach nor suggest the presently claimed methods for increasing apoptotic cell death and that this rejection of claims 6, 9, 11 and 24 under 35 USC §102(b) and/or 35 USC §103(a) may be properly withdrawn.

Claims 6, 9 and 10 stand rejected under 35 USC §102(b) as being anticipated by Ohga et al. (Cancer Res. 1996, 56:4224-4228). This rejection is respectfully traversed.

Ohga et al. describe studies in which a construct including almost full-length antisense YB-1 was introduced into a human epidermoid cell line called KB in order to establish two stable cell lines having reduced concentrations of YB-1. These cell lines were then shown to have increased sensitivity to various DNA-damaging agents. Ohga et al. do not report observing increased apoptosis on introduction of the antisense YB-1 construct into the KB cells. Indeed, if increased apoptosis had occurred, they would not have been able to establish the stable cell lines having reduced YB-1 and use those cell lines in subsequent studies. The KB cell line used by Ohga et al. is not a well known line and therefore the genotype is not generally known, however it appears likely that, as with the HeLa cell line, the KB cell line has a compromised p53 apoptosis pathway.

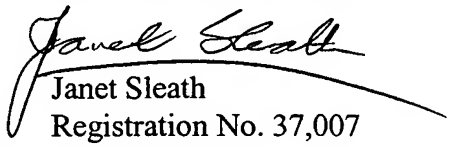
Applicants submit that Ohga et al. neither teach nor suggest the presently claimed methods for increasing apoptosis and that Ohga et al. in fact teach away from the presently

claimed invention. It is thus urged that this rejection of claims 6, 9 and 10 under 35 USC §102(b) may be properly withdrawn.

Concluding Remarks

A request for a one month extension of time, extending the deadline for response to Sunday, January 30, 2005, is being filed herewith. Favorable reconsideration and early allowance of the subject patent application is respectfully requested.

Respectfully submitted,



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Date: January 31, 2005
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